THROMBOTIC MICROANGIOPATHY (TMA)

TERM DEFINITION

Group of rare disorders characterized by thrombocytopenia, microangiopathic hemolytic anemia, and thrombus formation, leading to tissue injury.

CLINICAL DEFINITION

Microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ injury

PATHOLOGICAL DEFINITION

Occlusive thrombus formation in microvessels

CLASSIFICATION

**Most frequent types of TMA*

PRIMARY

(No underlying disease)

- **Thrombotic thrombocytopenia purpura (TTP)***
- **Atypical hemolytic uremic syndrome (HUS)***
- Shiga toxin-producing Escherichia coli (STEC-HUS)

SECONDARY

- Malignant hypertension (HTN)
- Infection
- Systemic lupus erythematosis (SLE)
- Cancer
- Transplant
- Drugs

CLINICAL PEARLS

TMA should be considered a medical emergency.

First order of business is to rule out TTP, since it is treatable with plasma exchange.

Differential diagnosis includes HIT and DIC.

Suspect a diagnosis of STEC-HUS in those presenting after an episode of gastroenteritis with bloody diarrhea.

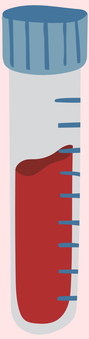
Suspect a diagnosis of aHUS by ruling out other causes of TMA, especially if renal failure present.

Suspect secondary TMA when patients present with TMA and compatible underlying condition.

Strictly speaking, the term *TTP* is limited to those patients with low ADAMTS13 levels. These patients almost always fall in the "**primary**" TMA category because they have no underlying disease. Beware of those who also apply the term *TTP* to patients with **secondary** TMA and a TTP clinical phenotype (e.g., neurological findings) despite normal ADAMTS13 levels.

HIT, heparin-induced thrombocytopenia; DIC, disseminated intravascular coagulation

DIAGNOSIS



CBC
- Anemia
- Thrombocytopenia

Peripheral smear
- Schistocytes

Hemolytic indices
- Elevated LDH
- Low haptoglobin
- Elevated AST
- Elevated indirect bilirubin

Establishing diagnosis of TTP
- High PLASMIC score*
- ADAMTS13 <5-10%

Establishing diagnosis of aHUS
- Diagnosis of exclusion
- Complement or genetic testing (not immediately available)

EVIDENCE OF ORGAN IMPAIRMENT

Troponin

BUN, creatinine

Brain imaging

ADAMTS13, ADAM Metallopeptidase With Thrombospondin Type 1 Motif 13

* *For clinical prediction sore, see https://harvardtma.partners.org/PLASMIC/*

TTP

Historical **pentad** (thrombocytopenia, MAHA, neurological and renal impairment, and fever) present in only 5% of patients.

Neurological > renal impairment

ATYPICAL HUS

Typically presents with **triad** of MAHA, thrombocytopenia (usually mild), and acute kidney injury.

Renal > neurological impairment

THERAPEUTIC PRINCIPLES

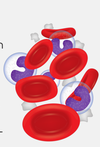
- If TMA suspected but diagnosis uncertain, start therapeutic **plasma exchange** (TPE) within 4-8 hours of presentation; TPE can be stopped if ADAMTS13 levels come back > 10%.
- If established TTP, continue treating with TPE.
- If aHUS, **eculizumab** (anti-complement 5) is first-line therapy of choice.
- If secondary TMA, discontinue inciting drugs or manage underlying systemic diseases.

PROXIMATE MECHANISMS

TMA occurs by different mechanisms according to the cause:

TTP - ADAMTS13 deficiency, which leads to accumulation of high molecular weight vWF multimers, which then lead to formation of platelet-rich thrombi.

aHUS - complement dysregulation with uncontrolled activation of the alternative pathway of the complement system, which leads to platelet and endothelial activation and platelet-rich thrombi.



(STEC)-HUS - Shiga toxin enters circulation from the GI tract and activates monocytes and neutrophils, leading to prothrombotic state.

Secondary TMA - pathogenesis poorly understood.

EVOLUTIONARY MECHANISMS

How has evolution made us vulnerable to developing TMA? For starters, we wouldn't develop TMA if our circulation was not closed, a step that took place in the ancestral vertebrate. Second, it would not occur without platelets, and in the case of TTP, von Willebrand factor (vWF) and ADAMTS13. Each of these factors also evolved with the dawn of vertebrates. This is an example of an **evolutionary trade-off** whereby benefits of closing our circulation (and using platelets and vWF to plug the holes) > risks of developing TMA.

In addition, **gene-environment** mismatch may account for **drug- and transplant-induced** TMA. STEC-HUS involves a longstanding interaction between host and pathogen which has certainly gone through many evolutionary iterations.

HISTORY OF MEDICINE

TMA was first described by Eli Moschcowitz in 1924 who described a case of acute febrile hemolytic anemia with petechiae and the development of neurological signs shortly before death. No further case was described until 1936, when a composite clinico-pathological study of four cases was published. Only then did interest in TMA (which at that time was synonymous with TTP) begin to pick up. Jump ahead to 1991 when a seminal paper was published in the New England Journal of Medicine showing that therapeutic plasma exchange increased survival in TTP from **10% to 90% - a true game changer!** ADMTS13 was first purified in 2001, leading to enormous advances in diagnostics.

NOTES

ATTRIBUTIONS

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The Blood Project
ENCYCLOPEDIA OF BLOOD